EXHIBIT 1

NAS Class Certification Expert Report by Dr. Lewis Rubin:

I, Lewis P. Rubin, M.Phil., M.D., file this report under penalty of perjury. I am a board-certified pediatrician and neonatologist (a pediatrician who specializes in disorders and care of newborns and infants). I am currently Professor of Pediatrics and Vice Chair for Research at Georgetown University Medical Center and MedStar Georgetown University Hospital, both located in Washington, DC. For more than three decades, I have worked as a clinician, a director of neonatology services, and a clinical and laboratory-based investigator in the fields of maternal/newborn normal and abnormal physiology; neonatal stress and nutrition; brain development; neuroprotection; and clinical trials. I have authored more than 100 peer-reviewed scientific publications and numerous reviews and textbook chapters. I have received national and international professional and scientific society awards and honors.

Since the mid-1980s, I have directly cared for hundreds of newborns who have been exposed to maternal drugs, including opioids, and have managed Neonatal Abstinence Syndrome (NAS) in several states. A decade ago, I served as the Co-Chair for the State of Florida Collaborative Substance Exposed Newborn Task Force, a joint initiative of the March of Dimes and Florida Coalition of Healthy Start Programs. My other qualifications are listed in my *curriculum vitae* which is attached as Exhibit A. For my work on this project I am being compensated at a rate of $600 per hour.

I have been asked to offer opinions regarding the diagnosis, management/treatment, and prognosis of infants who are diagnosed with Neonatal Abstinence Syndrome. In offering my opinions, I reviewed relevant medical literature, a plaintiffs' expert report, and other relevant case materials. The opinions I provide in this Report are held to a reasonable degree of medical and scientific certainty and are based on my education, training, experience, and review of the above-mentioned materials.

1. Diagnosis of NAS

Opioids are a class of natural, endogenous, and synthetic compounds that activate classes of opioid receptors in the central nervous system (CNS) and produce supraspinal (general) analgesia. Other acute effects of opioids can include sedation, euphoria, miosis (contracted pupils), respiratory depression, and decreased gastrointestinal motility. Neonatal Abstinence Syndrome (NAS) is a complex clinical syndrome (a group of signs and symptoms that occur together and characterize a particular condition); NAS can be variably expressed, both in types of signs and their severity, among different infants, and in the same infant over time.

NAS commonly refers to a postnatal withdrawal syndrome that can manifest shortly after birth in a proportion of infants who are born to women with opioid or other drug use during pregnancy. Opioid exposures include illicit opioids such as heroin, use or misuse of prescription painkillers, or maternal treatment medications such as morphine, methadone, or buprenorphine. Different

opioid-exposed infants may display unique features and either show no obvious neonatal effects or reside along a continuum of signs of withdrawal.[1]

An important point about NAS is its clinical scoring systems were designed specifically for neonatal withdrawal from prenatal exposure to *opioids*, but the term and diagnosis NAS is used more broadly, *i.e.,* when there has been prenatal exposure to non-opioid drugs including benzodiazepines, ethanol, or selective serotonin reuptake inhibitors (SSRIs).[2] In fact, for some clinicians, use of the term NAS has become conflated with a broader, more colloquial category of 'neonatal withdrawal syndrome', which describes abnormal findings in babies who have been prenatally exposed to a range of non-opioid drugs. This broader use of the diagnosis of NAS to mean any neonatal withdrawal syndrome has been codified in the current (10th) revision of the International Statistical Classification of Diseases and Related Health Problems (CD-10-CM) Code P96.1. This reference states: "Neonatal withdrawal or neonatal abstinence syndrome (NAS) is a withdrawal syndrome of infants, caused by the cessation of the administration of *licit or illicit drugs* [emphasis added]" (https://icd.codes/icd10cm/P961). Similarly, the previous medical coding and billing system, ICD-9, which was in use from 1978 to 1983 (and after), did not differentiate between presumed withdrawal from opioids and from other CNS stimulants or depressants, psychoactives, or other drugs.

Certainly, some signs and symptoms in infants prenatally exposed to different drugs can be overlapping and may be misinterpreted as a 'withdrawal syndrome.' A likely explanation for the broadened use of NAS is a general absence of clinical tools (*e.g.,* scoring or diagnostic systems) for describing these other non-opioid induced syndromes. As described below, the tools for NAS in its original, prenatal opioid exposure meaning sometimes have been used in these other situations, despite no evidence for their applicability. One result is the use of NAS to include both symptomatic opioid- and non-opioid-exposed infants can complicate interpretation of population and outcomes studies.

Finally, and for the above-mentioned reasons, NAS should be a considered as a diagnosis of exclusion; considering other diagnoses is important, because many infants with NAS may be at elevated risk for infections and other diagnoses that can present with similar non-specific signs, including CNS disorders. Consequently, a diagnosis of NAS (meaning a symptomatic infant) should be 'ruled-in' using maternal and/or neonatal toxicology screens (*e.g.,* from blood, urine, hair, meconium) and, if 'tox screen' results are not available, by obtaining a suggestive history of maternal opioid use.

The signs of NAS typically manifest one to three or more days after birth, depending on the type of opioid exposure, dosage, duration, and the most recent maternal dose. These signs can include CNS hyperirritability, poor sleep, increased arousal (*e.g.,* high-pitch cry), poor feeding, loose stools, vomiting, skin mottling, sweating, tachypnea (rapid breathing), and, in the most severe cases, seizures. However, the clinical presentation of NAS can vary both due to the above-mentioned factors as well as maternal drug history (including duration in pregnancy of exposure

and timing of the most recent use of drug before delivery), maternal metabolism, net transfer of drug across the placenta, placental metabolism, infant metabolism and excretion, and other factors not related to the opioid exposure *per se*, which include prenatal polysubstance exposure (*e.g.*, to nicotine, benzodiazepines, alcohol), genetic influences, and the specific drug pharmacokinetics.[3] Genetic factors likely account for some of the unexplained variability in NAS severity.[4]

Several scoring systems have been proposed in order to provide a more objective diagnosis of infants with NAS. The Finnegan Neonatal Abstinence Scoring System (FNASS) was developed by Dr. Loretta Finnegan and colleagues in 1975.[5] This tool, or shortened (modified) versions, by the 1980s became the most widely used assessment tool to measure the signs and severity of neonatal opioid withdrawal symptoms. Several other clinical NAS scoring systems were also developed at this time[6], but they have not gained wide acceptance in practice, despite the American Academy of Pediatrics 1988 statement, "Neonatal drug withdrawal"[7], which recommended using one of them, the Lipsitz tool (the Neonatal Drug Withdrawal Scoring System)[8]; this recommendation probably resulted from that tool's greater simplicity and purported good sensitivity for identifying clinically important withdrawal.[9] Nevertheless, the Lipsitz scoring system is rarely employed compared with the more comprehensive FNASS. Similarly, more recently proposed evaluation tools[10] have not yet replaced the FNASS.

It is important to note that, although the FNASS was originally designed to serve as a standardized scoring system *for research*, understandably it was rapidly utilized as a clinical tool by physicians and nurses who care for newborns who are at risk for opioid withdrawal.[11] The FNASS ranks severity of gastrointestinal, neurologic, and autonomic nervous system signs. Standard pediatric and neonatology practice for at-risk infants is, generally, whenever a newborn (or infant) attains a sufficiently high FNASS score, pharmacologic therapy is initiated. Twenty-one items relating to possible signs of withdrawal are monitored every two to four hours; NAS is generally diagnosed if the score is ≥8 on three consecutive scores or is ≥12 on two consecutive scores. Moreover, common practice is to use FNASS scoring as *the primary criterion* to guide decisions about how to initiate, maintain, and taper pharmacologic therapy. And, although marked variations in treatments for NAS still exist, the FNASS remains, by far, the most widely used tool to assess therapy.[12]

An important consideration in the evaluation of suspected NAS is that the FNASS and similar scoring systems, while they help to make diagnosis more uniform, have issues with consistency and reliability. Specifically, the scoring system has not been validated.[13] Moreover, the FNASS has not been shown to accurately or, with an acceptable degree of reliability, reflect the clinical condition of the newborn with NAS.[14] An additional drawback of the FNASS and similar tools is that the reporting of signs/symptoms by caregivers can be subjective, and inter-rater variation among nurses who administer the score may increase, and consequently the assessment of monitoring infants with NAS can suffer, unless there is frequent reinforcement of training about how properly to use the scoring tool.[15]

Further, the assessment tools cannot consider dyadic (mother/baby) communication and synchrony (*i.e.,* the mother's ability to read, interpret, and respond appropriately to infant cues and the ability of the infant to effectively relay needs to the mother). These are important aspects of neonatal functioning in the immediate postnatal period and beyond[16] and it is recognized that mother/infant interaction decreases the signs of NAS severity.

In sum, at present, there is no national consensus about which tool to use or the interval between assessments.[17] Related clinical uncertainties about NAS management include an unproven linkage of the FNASS to pharmacologic management of withdrawal symptoms, variations in accepted treatment thresholds, and occasional use of different cutoffs for diagnosis and/or treatment.[18] To these points, in 1975, Dr. Finnegan and her coauthors suggested that use of less ambiguous and redundant items might improve this tool.[19]

Another issue with NAS scoring systems for diagnosing NAS is they have been applied to non-opioid prenatal exposures. Several studies and reviews on "neonatal withdrawal" use Finnegan scoring to assess infants born to mothers who, for example, took cocaine or methamphetamines[20] or SSRIs[21]. In a recent Australian study, 18% of infants diagnosed with NAS (using ICD-10 code P96.1) had been exposed to non-opioid drugs.[22] This issue of a 'broader' use of NAS for infants who were not exposed to opioids was addressed above.

Putative 'withdrawal signs' also have long been described in infants who have prenatal exposures to non-opioids including benzodiazepines[23], barbiturates[24], alcohol[25], and SSRIs[26]. In general, polydrug or polysubstance exposure in instances of prenatal opioid use also can increase NAS severity.[27] However, although prenatal exposure to several drugs can cause non-specific signs in an infant, diagnosis of NAS due to prenatal opioid exposure requires a consistent clinical presentation (as captured in the Finnegan score items), confirmed maternal history of opioid use, if available, and toxicology screens.

2. Treatment of NAS

Due to the varied presentations of NAS, treatment options and duration must be individualized. Hospitals where these newborns receive care should maintain NAS guidelines for physicians and nurses and facilitate training in NAS diagnosis and proper NAS scoring and interpretation. Optimizing parental involvement and both investigating and supporting the household are important and, indeed, in many jurisdictions, are required.

Initial treatment of infants who develop early signs of withdrawal is directed at minimizing environmental stimuli (light, sound) by placing the infant in a dark, quiet environment; avoiding auto-stimulation by careful swaddling; responding promptly to an infant's signals; adopting appropriate infant positioning and comforting techniques; and providing frequent small volumes of hypercaloric formula or human milk to minimize hunger and allow for adequate growth. Pharmacologic treatment, most often with opioids, and sometimes with clonidine as an adjunct drug, is often begun early once FNASS scores sufficiently rise. Treatment with non-opioid

medications such as phenobarbital or benzodiazepines, once common, has been shown to be an inferior strategy and is no longer recommended. Among opioid treatments, in recent clinical trials, methadone has been shown to provide more effective treatment than morphine[28] and buprenorphine treatment may shorten NAS hospitalizations[29]. Also, recently there has been renewed focus on non-pharmacologic strategies in NAS treatment, such as the so-called 'Eat, Sleep, Console' (or ESC) approach.[30] ESC and similar approaches are being used to limit pharmacologic treatment and shorten hospital length of stay. Similarly, parental involvement and rooming-in with NAS infants has beneficial impact[31]; even after adjusting for breastfeeding, parental presence significantly reduces NAS scores and opioid treatment days[32].

3. Longer-term prognosis in children who were diagnosed with NAS

Follow-up and neurodevelopmental evaluation of prenatally opioid-exposed infants have been conducted for several decades but, admittedly, the findings remain uncertain. One of the difficulties is that infant and childhood development is strongly influenced by the home, parental involvement, and other environmental factors. Considering these influences means that the further a child is in time from a prenatal exposure, the more difficult cause ascertainment becomes. Some clinical studies have suggested lower school function or motor delays can occur in children with prenatal opioid exposure. However, major confounders in these studies include the postnatal environment, prenatal polysubstance use, suboptimal follow-up, and reliance on maternal reporting of substance use, all of which preclude definite conclusions about the effect of prenatal opioid exposure and NAS on long-term outcomes. In one example, a linkage study between universal maternal drug test results and pediatric follow-up care documented in electronic health records in an Ohio county showed increases in some diagnoses among the prenatal opioid-exposed children.[33] However, the much higher hepatitis C exposure rate for the opioid-exposed group (6.8% vs 0.1%) provides one indication that other, unassessed major risk factors (parental illicit drugs, risk-taking behaviors, lower SES) would affect the children's outcomes.

Despite these considerations, the several months to several years follow-up of these children is encouraging regarding outcomes. Controlled data strongly suggest that most children who have experienced NAS will develop normally, gauged by a broad range of measures of cognitive and social functioning.[34] In another recent uncontrolled study (*i.e.*, no equivalent comparison group), neurodevelopmental assessment at two years in children who had NAS showed slightly but significantly lower scores than in controls, but the Bayley Neurodevelopmental Score Developmental Quotients were in *the normal range*.[35] A comment on this publication[36] illustrates the difficulties in attributing prenatal opioid exposure to abnormal infant and childhood outcomes. These authors pointed out the problems inherent to a retrospective chart review[37] and listed weaknesses in the analysis including ignoring deleterious effects of the intrauterine environment in women who have Opioid Use Disorder (OUD: toxic stress, dehydration, inadequate nutrition, violence/trauma, psychiatric issues, tobacco or alcohol or other drug use, other medications known to alter neurodevelopment) and the large standard errors in the data, which prevent drawing conclusions.

One of the earlier reports, a 1988 study of 14 severely affected opioid-exposed infants, *i.e.,* who had withdrawal-associated seizures, 12 were available for evaluation at one year of age.[38] Neurologic examinations were normal in 9 of the 12 infants evaluated. EEG results were abnormal in 9 neonates; however, subsequent EEGs for 7 of 8 of these infants normalized during follow-up. Mean comprehensive neurodevelopmental testing (Bayley Scales of Infant Development) were also normal by one year of age, which was similar to matched controls that were drug exposed, but in whom withdrawal-associated seizures did not develop.

A recent evaluation of 5-8-month outcomes in 78 opioid-exposed infants from a prospective cohort study showed "little-to-no effect of MAT [medication assisted therapy] and pharmacological treatment of NOWS on infant neurodevelopment and behavioral outcomes".[39] In terms of prenatal exposure, methadone and buprenorphine have been shown to be sufficiently safe and effective for prescription in pregnancy (for mother and fetus) and child.[40]

There are several important cautions for evaluating and determining potential long-term effects of fetal and neonatal opiate exposure. (Neonatal exposure usually is a result of either opioid treatment for NAS or opioid administration, e.g., fentanyl infusions, to ill infants in intensive care units.[41]).

The first caution arises from the recent historical example of prenatal cocaine exposure. Beginning in the late 1970s, amid markedly increased cocaine and crack cocaine use, numerous infants were exposed to cocaine *in utero*; the popular press coined the term 'crack baby.' Early studies on outcomes of these infants, which reported on small sample sizes and were not able to account for confounding factors, suggested many of these infants would be severely emotionally, mentally, and physically disabled, with attendant lifelong strains on medical and social services. However, later studies have failed to substantiate these findings of common severe, disabling consequences.[42] In effect, the initial concerns appear to have been vastly overstated. Although cocaine use can induce specific problems of pregnancy (including placental abruption, preterm labor and birth, low birth weight), transient neurological findings in newborns, and, controversially, minor behavioral findings, most people who were exposed to cocaine prenatally do not have disabilities and should not receive a biological or social stigma.

The second caution when determining outcomes involves confounding factors that interact with prenatal opioid exposure. These include polysubstance exposure, maternal trauma/depression, socioeconomic factors, and genetics. Data are difficult to interpret because of the influence of children living in households where one or both parents uses drugs, poverty, neglect, dysfunctional caregivers, and parental co-morbidities that stem from psychiatric disorders.

Pregnant women who self-medicate with opioids may also use alcohol. Unlike opioid exposure, alcohol is a known fetal toxin and teratogen (substance inducing birth defects) and causes fetal alcohol spectrum disorder (FASD) including a severe form known as fetal alcohol syndrome (FAS)[43], characterized by an abnormal face, small head size, and cognitive, neurosensory, and behavioral problems. Other drugs of abuse also may cause neonatal and/or long-term

complications. Prenatal amphetamine exposure may precipitate neonatal irritability and, perhaps, subtle longer-term effects.[44] Recent reports raise concerns about cannabis use in pregnancy.[45] SSRIs, which include Prozac, Paxil, Zoloft, and others, are the most frequently prescribed drugs to treat depression in the general population and in pregnant women[46] and can cause abnormal signs in newborns.

A theme that has long been appreciated in the care and follow-up of children who had NAS is the importance of the socioeconomic and psychosocial dimensions of families. The relevant factors include parental drug seeking activity, alcohol and tobacco use, child neglect, poverty, and foster placement.[47] To this point, in my clinical practice, I stress for families the importance of these associated parental health, lifestyle, and psychosocial factors over the prenatal opioid exposure *per se*.

I reserve the right to amend or supplement this report and my opinions based upon newly or later acquired information.

Lewis P. Rubin, M.D.

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